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Invited Review Article

Cardiovascular-Kidney-Metabolic (CKM) syndrome: A state-of-the-art review☆

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ABSTRACT

The correlation between obesity, type 2 diabetes mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD) is an escalating and widely acknowledged epidemic in industrialized nations. Recently, this complex web of interrelated health conditions has been collectively defined as the Cardiovascular-Kidney-Metabolic (CKM) syndrome by the American Heart Association (AHA). The molecular mechanisms underlying CKM disease contain a spectrum of interconnected factors, including hyperglycemia, insulin resistance, heightened activity of the renin-angiotensin-aldosterone system (RAAS), the generation of advanced glycation end-products, oxidative stress, lipotoxicity, endoplasmic reticulum stress, abnormalities in calcium handling, malfunctioning of mitochondria and impaired energy production, as well as persistent chronic inflammation. Addressing their prevention, management, and treatment is of paramount importance to promote better patient health outcomes. The objective of this review is to provide a comprehensive and critical examination of the current state-of-the-art regarding the recently defined CKM syndrome. This includes an exploration of epidemiological evidence establishing connections between cardio-renal-metabolic diseases, an examination of the underlying patho-physiological mechanisms, and a comprehensive overview of existing treatment modalities.

Introduction

According to extensive evidence, type 2 Diabetes Mellitus (DM), cardiovascular disease (CVD), and chronic kidney disease (CKD) represent three major health challenges associated with substantial morbidity and mortality. It is considered that these conditions frequently coexist.[1] Based on the National Health and Nutrition Examination Survey (NHANES) dataset from 2017 to March 2020, the prevalence of CVD, including congenital heart disease, heart failure (HF), stroke, and hypertension, among adults aged 20 and older, stood at an overall rate of 48.6 %, which corresponds to 127.9 million individuals in 2020. This prevalence also exhibits an increase with advancing age in both males and females. In the American Heart Association's (AHA) 2023 heart disease and stroke statistics update, CVD accounted for roughly 19.05 million global deaths in 2020.[2,3] The international collaboration on the global burden of CKD reported a significant 41.5 % increase (with a 95 % uncertainty interval of 35.2 to 46.5) in all-age mortality rates from CKD

☆ Interplay of CVD, CKD, and metabolic disease.

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between 1990 and 2017.[4] Furthermore, the global prevalence of diabetes in individuals aged 20 to 79 in the year 2021 was estimated to be 10.5 %, equivalent to 536.6 million people, and this is projected to rise to 12.2 %, encompassing 783.2 million individuals, by the year 2045.[5]

The epidemiological data from observational studies and clinical trials provide substantial evidence of a significant overlap between metabolic, cardiovascular, and renal diseases. In recognition of this intricate relationship, the American Heart Association (AHA) has recently introduced the concept of a combined disease condition known as Cardiovascular-Kidney and Metabolic Syndrome (CKM), highlighting the close associations and interplay between these three health domains (CVD, CKD, and Type 2 DM) (Fig. 1).[6] In the most recent presidential advisory note by AHA, the various stages of CKM were discussed with a significant emphasis on the pivotal role of screening and addressing social determinants of health and its impact on the overall well-being of individuals dealing with CKM.[6,7] Several other mechanisms are intricately involved in CKM, which serve as a foundation for the therapeutic management of this emerging condition. This review is an in-depth analysis of the potential mechanisms involved in CKM and explores the therapeutic approaches available for effectively handling this complex syndrome. Additionally, we emphasize the importance of interdisciplinary collaboration in actively preventing CKM syndrome and advancing the holistic health and well-being of individuals affected by this condition.

Epidemiological evidence of CKM disease connections

CVD is the leading cause of mortality in the United States, regardless of individuals' self-determined racial or ethnic backgrounds.[8] Notably, CVD remains the common cause of mortality, accounting for 43.6 % of all deaths among individuals with end-stage renal disease.[9] There are several contributing risk factors that play a substantial role in the morbidity and mortality related to CVD, and these factors are collectively known as cardiometabolic risk factors.[8,10,11] Cardiometabolic risk refers to a complex array of interconnected traditional risk factors associated with metabolic syndrome (MetS). These factors include dyslipidemia, hypertension, obesity, insulin resistance, hyperglycemia, and behavioral factors like physical inactivity, smoking, and unhealthy dietary patterns. Moreover, it incorporates non-modifiable risk factors such as family history, age, sex, and race/ethnicity, which contribute to an individual's susceptibility to CKM syndrome.[10]

In 2021, the International Diabetes Federation estimated that about 537 million people aged 20-79 years had diabetes, representing approximately 11 % of the global population. They further projected a substantial increase, anticipating the number to reach 783 million by the year 2045.[5] Prospective studies, mainly conducted in Western and other high-income countries, consistently indicate that the risk of CVD is at least twice as high in people with diabetes compared to those without diabetes. In a cohort study of approximately 1.2 million people with type 2 DM from various countries, including England, Germany, Japan, the Netherlands, Norway, and Sweden, the evaluation of those initially without concomitant CVD or CKD revealed that 24 % of first events were heart failure, stroke (16 %), myocardial infarction (14 %), PAD (10 %) and 36 % were CKD.[13] In the Japanese population within this study, 31 % of the first events were heart failure, and 39 % were CKD.

Epidemiological studies have indicated a multifaceted association with CKM syndrome. In a claims-based observational cohort study that focused on adults with type 2 DM but no prior history of CVD or CKD who began their first-line oral antidiabetic drug therapy between 2008 and 2018, the study found that 24 % of the initial events observed were related to HF and 36 % were connected to the development of CKD.[14] Arnold et al. conducted a study aimed at evaluating the prevalence of cardio-renal-metabolic conditions and their co-occurrence among a substantial cohort of 530,747 adults with type 2 DM in the United States. This study utilized data from

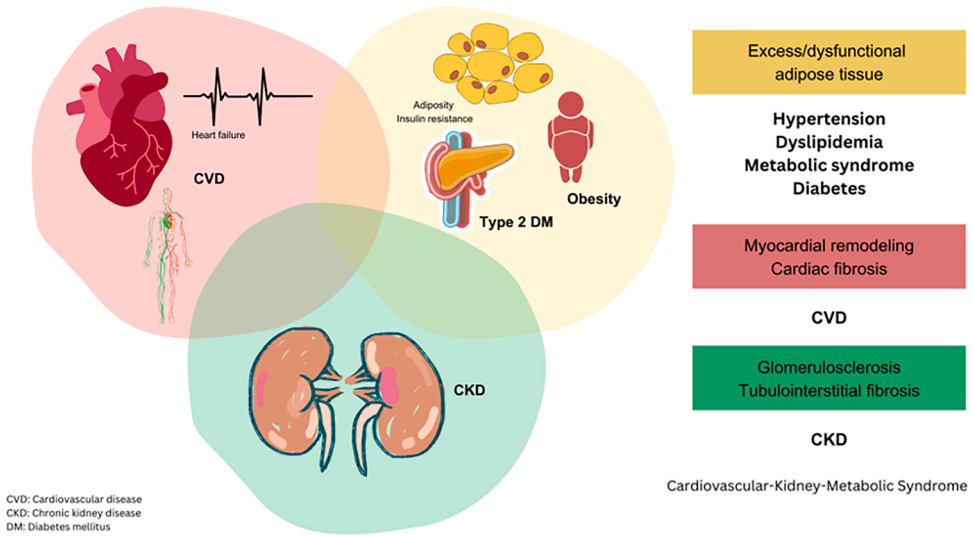

Fig. 1. CKM syndrome.[1,6]

a USA-based outpatient registry comprising 271 healthcare offices specializing in primary care, cardiology, and endocrinology.[15] The study findings revealed that it was relatively unusual for patients to have isolated type 2 DM without any concurrent CKM conditions, with only 6.4 % of individuals having type 2 DM as their sole health issue. On the other hand, a significant portion of the participants, approximately 51 %, had three or more other CKM conditions. The most frequently observed combinations among these conditions included various groupings of hypertension, hyperlipidemia, CVD, and CKD.[15]

In a recent study by Ostrominski et al., the researchers investigated the prevalence and impact of overlapping cardio-renal-metabolic conditions among patients with these health issues.[16] The findings of this study indicated that the risk of experiencing primary outcomes increased as the level of overlap among cardio-renal-metabolic conditions increased. Mainly, individuals with all three CKM conditions experienced the highest risk of primary events, with an adjusted hazard ratio (HR) of 2.16 (95 % confidence interval: 1.72-2.72), compared to those with HF alone.[16] Indeed, these findings highlight the critical importance of comprehending the interconnections between cardiovascular, renal, and metabolic diseases and the need to implement effective preventive strategies to address these complex and interrelated health concerns.

Cardio-renal-metabolic disease connections: pathophysiology and mechanisms

The pathophysiology of CKM syndrome is characterized by a complex interplay of hemodynamic and neurohormonal mechanisms, including sympathetic overactivity, the renin-angiotensin-aldosterone system, various chemical mediators (nitric oxide, prostaglandins, endothelins, etc.) and oxidative stress.[1,11] The molecular mechanisms through which diabetes impacts the cardiovascular and renal systems are indeed complex and involve a range of interconnected pathways (Fig. 2). In hyperglycemic states, the excessive influx of glucose into cells leads to the production of mitochondrial superoxide, which results in an exacerbation of oxidative stress.[11,17] This is postulated as the primary initiating event in diabetes-induced organ damage. The increased reactive oxygen species (ROS) production causes tissue damage through several mechanisms, including activation of the polyol and hexosamine pathway, which exacerbate oxidative stress in a vicious circle—activation of protein kinase C (PKC), formation of advanced glycation end-products (AGEs), resulting from non-enzymatic glycation of proteins, and upregulation of their cellular receptor RAGE.[11,17–19] In turn, AGEs can directly damage the heart, blood vessels, and kidneys. They cause cross-linking of matrix proteins, increasing tissue stiffness. Consequently, AGEs are intricately involved in the pathogenesis of diabetes-related organ damage, including conditions like diabetic cardiomyopathy, diabetic kidney disease (DKD), and atherosclerosis. AGEs and ROS are also closely associated with endothelial dysfunction, and this dysfunction is a significant contributor to diabetic microvascular and macrovascular complications.[11,18,19] Moreover, hyperglycemia is associated with the activation of the local RAAS within the myocardium and the kidneys. This activation of RAAS can have several detrimental effects on both organs, promoting vasoconstriction, fibrosis, and the exacerbation of organ dysfunction.[20]

Additional mechanisms that contribute to cardiovascular and kidney disease in type 2 DM include endoplasmic reticulum (ER) stress, abnormal calcium handling, oxidative stress, and chronic inflammation.[11] ER stress has been implicated in various detrimental processes, such as cardiomyocyte apoptosis, atherosclerosis in individuals with diabetes, and the progression of diabetic kidney disease.[18] Oxidative stress plays a significant role in the development of CKM syndrome, which is mentioned earlier.[21,22] ROS are naturally produced in the body to promote essential cellular signaling and maintain physiological responses. Free radical formation is generally divided into the generation of ROS or reactive nitrogen species (RNS) known to regulate cell growth and differentiation, smooth muscle relaxation, and inhibition of platelet adhesion.[23] However, when there's an imbalance in redox homeostasis, it leads to a proinflammatory and profibrotic environment. This environment, in turn, contributes to disruptions in insulin metabolic signaling, diminished endothelial-mediated vasorelaxation, and a range of structural and functional abnormalities involving the cardiovascular and renal systems.[21,22]

Emerging research indicates that overnutrition, characterized by the excessive consumption of high-fat and high-carbohydrate foods and the presence of aldosterone and angiotensin II (ANG II), can promote insulin resistance.[21] This is achieved through the activation of the mammalian target of the rapamycin (mTOR)/S6 kinase 1 (S6K1) signaling pathway in cardiovascular tissue and the kidney, thereby contributing to the intricate connection of CKM syndrome.[21] A recent preclinical study conducted by Pulakat et al. reported that S6K1 is activated in the cardiovascular tissue of a rodent model subjected to overnutrition.[22] This activation is associated with reduced insulin metabolic signaling and has various adverse effects, such as impaired nitric oxide (NO)-mediated vascular relaxation, cardiac diastolic dysfunction, and the promotion of kidney tubulointerstitial fibrosis.[22,23] These multifaceted mechanisms collectively play significant roles in the development and exacerbation of cardiovascular and renal complications in the context of type 2 DM. Understanding these processes is essential for designing effective strategies to prevent and manage these complications.

Stages of CKM

The intersection of various aspects of CVD, kidney disease, Type 2 DM, and obesity highlights the importance of a holistic approach in comprehending and addressing these interlinked health conditions. According to the presidential advisory note released by AHA in early October 2023, CKM disease is categorized into four distinct stages, from stage 0 to stage 4 (Table 1).[6]

These stages likely signify diverse levels of progression and severity within the intricate spectrum of this disease. Each stage demands individualized management and interventions to effectively tackle the specific challenges and complications linked with CKM disease. Stage 0 of the CKM disease classification is designed for individuals who currently have no identifiable risk factors for CVD, kidney disease, or metabolic disease.[6] The primary objective at this stage is preventive in nature, with a focus on primordial prevention and maintaining cardiovascular health by adhering to the eight recommended health behaviors outlined by AHA. These behaviors,

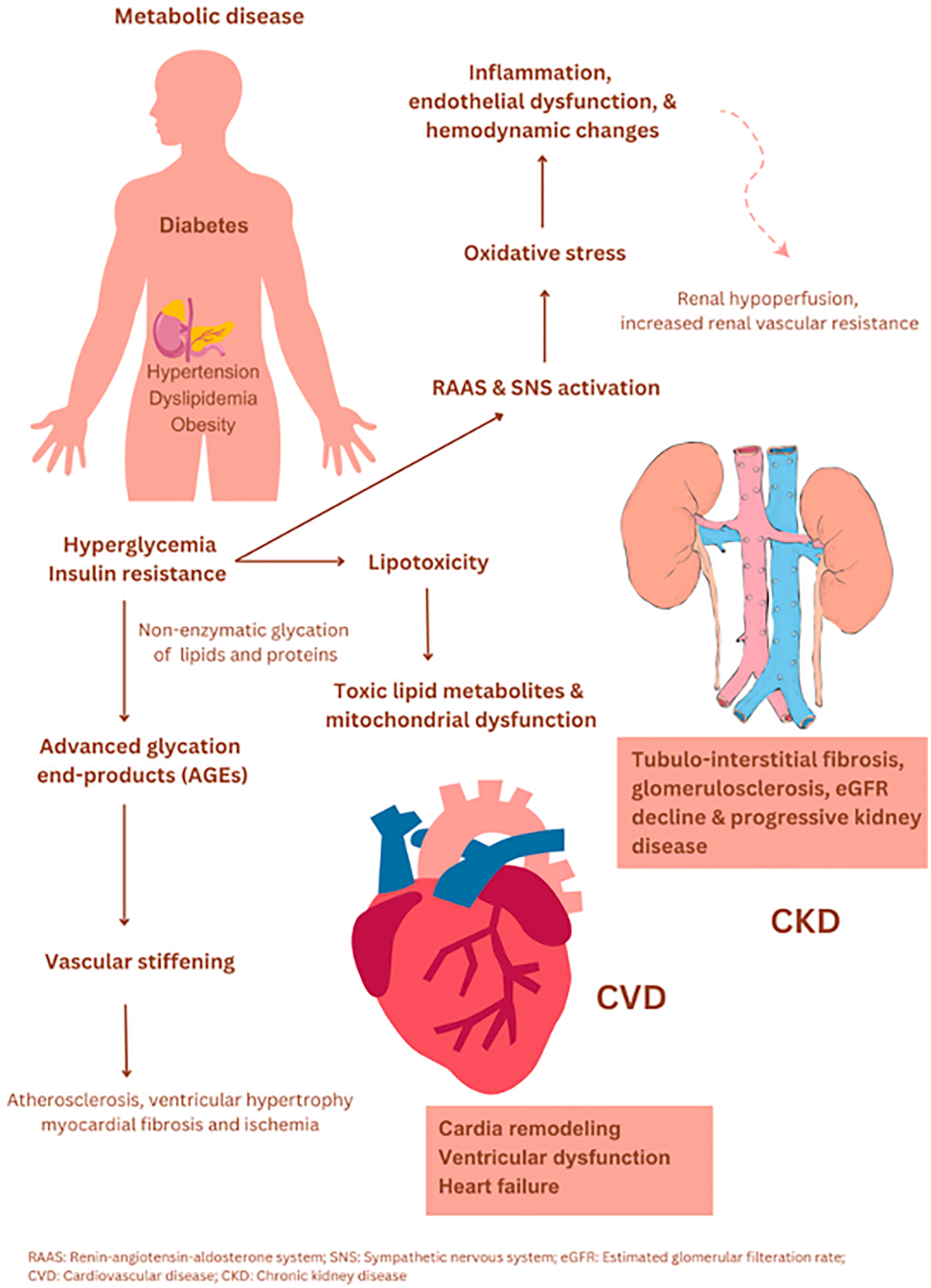

Fig. 2. Interplay of CVD, CKD, and metabolic disease.[1,11(1)]

referred to as "Life's Essential 8," comprise being more active, quitting tobacco, getting healthy sleep, managing weight, controlling cholesterol, and managing blood sugar and blood pressure.[24]

(1) The figure illustrates the intricate pathophysiology that underlies the complex interplay of cardiovascular, kidney, and metabolic components in the CKM syndrome. Overall, the presence of excessive and dysfunctional adipose tissue often gives rise to metabolic risk factors, including hypertension, hypertriglyceridemia, metabolic syndrome (MetS), and type 2 DM, as well as CKD. The cumulative effect of these conditions over time leads to the development of subclinical coronary atherosclerosis, observable through coronary artery calcification and fine irregularities in myocardial structure and function. Simultaneously, there is an incremental decline in kidney function, increasing the susceptibility of individuals to an elevated risk of clinical CVD, kidney failure, disability, and mortality, thus the progression to CKM syndrome. Created with BioRender.com

Table 1
Stages of CKM.[6]

Stages	Definition	Recommended Interventions
Stage 0 *No Risk Factors*	Individuals with no CVD, kidney disease, and metabolic disease risk factors.	• Healthy eating, physical activity and regular sleep habits • Avoid nicotine use and cigarette smoking • Maintain optimal weight • Manage blood pressure, blood sugar and cholesterol levels based on age-specific criteria • Screen adults in stage 0 every three to five years to assess blood pressure, triglycerides, HDL cholesterol and blood sugar
Stage 1 *Excess/ Dysfunctional Adipose Tissue*	Individuals with excess body fat and/or an unhealthy distribution of body fat, such as abdominal obesity, and/or impaired glucose tolerance or prediabetes. [Defined as BMI $\geq$ 25 kg/m^2 (or $\geq$ 23 kg/m^2 for individuals of Asian ancestry), waist circumference $\geq$ 88/102 cm in women/ men (or $\geq$ 80/90 cm for individuals of Asian ancestry), fasting blood glucose $\geq$ 100–124 mg/dL or HbA1c between 5.7 % and 6.4 %.]	• Healthy eating and regular physical activity • 5 % weight loss • Treatment for glucose intolerance if needed. • Screening every two to three years is advised to assess blood pressure, triglycerides, cholesterol and blood sugar.
Stage 2 *Metabolic Risk Factors and CKD*	Individuals with type 2 DM, high blood pressure (hypertension stages 1 and 2), high triglycerides (hypertriglyceridemia $\geq$135 mg/dL), MetS, kidney disease.	• Sodium-Glucose Transport Protein 2 (SGLT2) inhibitors • Glucagon-like peptide 1 receptor agonists (GLP-1 RA) • Yearly assessment of blood pressure, triglycerides, cholesterol, blood sugar and kidney function.
Stage 3 *Subclinical CVD in CKM*	Early CVD without symptoms (subclinical heart failure or subclinical atherosclerosis) in people with metabolic risk factors or kidney disease or those at high predicted risk for CVD.	• In individuals with subclinical atherosclerosis Ø If coronary artery calcium (CAC) >0: Statin use is recommended in intermediate risk. Ø If CAC >100: Aspirin use is recommended, if low bleeding risk. Also, favors other agents for Atherosclerotic cardiovascular disease (ASCVD) risk reduction based on CKM profile. • In individuals with subclinical heart failure Ø Patients with ejection fraction <40 %: Angiotensin-converting enzyme inhibitors (ACEIs)/ Angiotensin 2 receptor blockers (ARB), Beta blockers. Ø Patients with diabetes: SGLT2 Inhibitors.
Stage 4 *Clinical CVD in CKM* (Stage 4a: no kidney failure Stage 4b: kidney failure present)	Symptomatic CVD/clinical CVD in people with excess body fat, metabolic risk factors or kidney disease. That is, patients with CKM syndrome with existing CVD.	• Individualized treatment for CVD based on CKM profile Ø In case of heart failure: Guideline-directed medical therapy (GDMT) for all patients. Ø For ASCVD: Prescribe aspirin and high-intensity statin for all patients; consider adding ezetimibe and PCSK9 inhibitors based on (low-density lipoprotein) LDL levels or high-risk ASCVD presence.

In stage 1, individuals demonstrate risk factors such as excess body fat, unhealthy fat distribution (e.g., abdominal obesity), impaired glucose tolerance, or prediabetes. The primary focus here is to provide support for healthy lifestyle changes, emphasizing the significance of adopting a balanced diet and engaging in regular physical activity to mitigate these risk factors.[6] In stage 2, individuals present with type 2 diabetes, high blood pressure, elevated triglycerides, or kidney disease, signaling an elevated risk for worsening kidney and heart conditions. The care objective in this stage is to address these risk factors actively, striving to prevent progression to CVD and kidney failure. Stage 3 encompasses early CVD in individuals with metabolic risk factors, kidney disease, or a high predicted risk for CVD, focusing on preventing progression to symptomatic CVD and kidney failure.[6] Stage 4, targeting symptomatic CVD in those with excess body fat, metabolic risk factors, or kidney disease, is further classified into (4a) for individuals without kidney failure and (4b) for those with it. Here, the focus is tailored treatment for CVD, taking into account specific conditions associated with CKM syndrome.[6]

Furthermore, numerous other factors contribute to the heightened likelihood of progressing across CKM stages, thereby increasing the risk for CVD and kidney failure. They are defined as risk-enhancing factors in the presidential advisory from the AHA on CKM syndrome.[6] These risk-enhancing factors encompass membership in (such as individuals of South Asian ancestry and those with low socioeconomic status), a family history of diabetes or kidney failure, sleep disorders, mental health conditions, chronic inflammatory disorders, sex-specific risk enhancers (including premature menopausal transition, adverse pregnancy outcomes, and polycystic ovarian disease), and an increased burden of adverse social determinants of health (SDOH).[6] Ethnic differences in CKM risk are attributable to genetic variation. Genetic factors may contribute to interethnic variations in diabetic kidney disease, with a higher prevalence observed in Asians compared to Europeans.[25] Additionally, genetic variation may play a role in the differences in CVD complications of type 2 DM between Asians and non-Asians. Studies have identified various genotypes significantly associated with CVD in Asians with type 2 DM, including Japanese, but not in Whites.[25,11] These associations include alleles encoding proteins involved in glucose and lipid metabolism. Gene-environment interaction is another fascinating factor influencing CKM disease phenotype, where environmental exposures modify genetic effects on disease risk. While commonly linked to temperature, pollutant exposure, and sociodemographic factors, other elements like age, gender, smoking habits, and biophysical parameters are also considered environmental factors. Studies suggest that genes like ENPP1, AP2A2, and the 9p21 locus may interact with type 2 DM to contribute to CVD in Asian populations.[26] These genes are involved in hormonal regulation of glucose metabolism, energy and lipoprotein metabolisms, and cell cycle regulation, respectively. The

utility of genetic risk identification for CVD lies in personalized medicine, where a genetic risk score can predict the likelihood of future CVD events, especially considering their connections with kidney and metabolic diseases. Various genetic variants contribute to this risk, and a polygenic risk score (PRS) can be constructed using different approaches.[26] Despite the current lack of comprehensive understanding of many genes' mechanisms contributing to the disease, these gaps present potential avenues for future research. This research could further enhance molecular understanding, particularly in the context of CVD in type 2 DM and its connections with the broader CKM syndrome, or reveal novel therapeutic targets.

Management of CKM syndrome

Lifestyle modifications

Obesity stands out as a key catalyst for the CKM and cardiometabolic risk epidemic. Consequently, a pivotal element of any prevention program targeting the reduction of CKM syndrome is the implementation of comprehensive therapeutic lifestyle modifications, emphasizing physical activity promotion, dietary control, and weight loss.[10] In the Framingham Heart Study cohort, an increase in weight of 2.25 kg or more over 16 years correlated with a 21 % to 45 % rise in the risk of developing MetS.[27] Effective management strategies for MetS involve aggressive lifestyle modifications and increased physical activity focusing on weight reduction.[27,28] A 15-year follow-up study demonstrated that young adults maintaining stable body weight experienced minimal progression of risk factors and lower MetS incidence.[29] Conversely, individuals with an increased body mass index during the follow-up period showed a higher incidence of impaired glucose tolerance and type 2 DM compared to those with stable or decreased body mass index. Even a moderate weight reduction induced by a very low-calorie diet resulted in substantial improvements in systolic/diastolic blood pressure, glucose, triglycerides, and total cholesterol at four weeks. Furthermore, greater weight loss achieved through lifestyle modification was associated with a more significant reduction in MetS prevalence.[28] The type and total amount of fat intake are essential considerations, given the correlation between blood lipid concentration and arteriosclerosis progression. Excessive carbohydrate consumption, converted to fat, can elevate triglycerides and reduce high-density lipoprotein (HDL) cholesterol; therefore, patients with MetS are advised to reduce carbohydrate intake.[30] While vitamin intake is believed to slow vascular aging through its antioxidative effect, studies confirming the preventive effect of CVD through vitamin intake are limited.[31] The Dietary Approaches to Stop Hypertension (DASH) diet promotes the inclusion of fresh vegetables, fruits, low-fat dairy products, brown rice, whole grains, fish, and lean chicken. This dietary pattern has demonstrated a significant reduction in systolic blood pressure levels.[28] Implementing these dietary approaches can disrupt the interplay between cardiometabolic and renal connections. Additionally, these approaches can foster weight loss, effectively halting the progression of CKM syndrome.

There exists an inverse correlation between the total volume of moderate-intensity exercise and the incidence or mortality of CVD. This relationship becomes more pronounced with higher levels of exercise volume.[32] A study conducted in the United States reveals that physical activity levels persist below the optimal threshold, indicating that approximately 60 % of all adults do not meet recommended activity levels, and a quarter abstain from physical activity entirely.[33] Moreover, 14 % of the youth report not participating in any recent physical activity.[33] Based on available evidence, it is recommended to participate in a minimum of 150 minutes per week of moderate-intensity exercise, which may include activities like brisk walking, biking at a speed of at least 8 kilometers per hour, engaging in active yoga, or participating in light swimming. Alternatively, dedicating more than 75 minutes per week to high-intensity exercises, such as jogging, running, cycling at a speed of at least 15 kilometers per hour, playing tennis, or engaging in intensive swimming, is advised to proactively prevent CVD. It is noteworthy that a negative dose-response relationship exists between the level of physical activity and the prevalence of metabolic syndrome (MetS). Engaging in exercise and increasing physical activity has been shown to decrease waist circumference, blood pressure, and body fat mass, while also improving insulin resistance and lipid profiles. For primary prevention of obesity, approximately 150–250 minutes of moderate-intensity exercise per week, along with an energy expenditure equivalent to 1,200 to 2,000 kcal per week, can effectively help prevent weight gain. To facilitate significant weight loss and prevent weight regain post-successful weight loss, it is advised to involve in recommended amounts of physical activity.[28,32] For weight loss, a range of 225–420 minutes per week is advised, while for weight maintenance after successful loss, the suggested duration is 200–300 minutes per week.[34] Both aerobic and strength exercises play pivotal roles in achieving these goals. Aerobic exercise significantly reduces the risk of CVD, and resistance exercise not only enhances physical function but also lowers blood glucose and blood pressure.[28,35] As exercise alone may be less effective in weight loss, combining it with an appropriate calorie-restricted diet is necessary. Indeed, the synergy of strategic physical activity, dietary control, and integrated weight loss strategies can effectively impede the development and progression of cardio-metabolic-renal disease connections. This comprehensive approach addresses multiple facets of health, promoting overall well-being and potentially mitigating the risk factors associated with CKM syndrome.

Cognitive-behavioral therapy (CBT) also plays a crucial role in modifying lifestyle behaviors and promoting adherence to a healthy lifestyle. Research indicates that behavior patterns established during childhood often persist into adulthood, emphasizing the long-term impact of environmental and genetic factors on lifestyle choices.[28,36] In the context of preventing MetS, the role of primary healthcare providers becomes particularly significant in delivering CBT. Medical professionals should prioritize building positive, consistent relationships with patients, taking into account their medical condition, life environment, knowledge level, experiences, and long-term interests. A deep understanding of these factors enables healthcare providers to tailor counseling and promote desirable behaviors that are specifically suited to each patient.[36] By maintaining ongoing engagement and understanding the individual nuances of a patient's life, motivation for adopting and sustaining positive lifestyle changes can be successfully achieved through cognitive-behavioral interventions. These interventions are emerging as valuable supplementary modalities in the comprehensive management of CKM syndrome.

Medical management

According to the most recent presidential advisory from the CKM Health Scientific Advisory Group, the algorithms for stages 0 through 3 of CKM primarily concentrate on preventing CVD events. In contrast, the algorithms for stage 4 of CKM prioritize the management of CVD within the context of CKM factors (Table 1).[6] Based on compelling evidence, adopting a comprehensive therapeutic approach addressing comorbidities associated with cardiovascular, kidney, and metabolic (CKM) conditions can yield synergistic benefits, leading to notable enhancements in patient outcomes.[1] Extensive data from large-scale clinical trials consistently demonstrate that the favorable impacts of novel glucose-lowering medications, including SGLT2 inhibitors and GLP-1 RA, extend beyond mere glycemic control. These drugs exhibit significant efficacy in reducing critical cardiovascular and renal endpoints, particularly in populations affected by type 2 DM.[37,38] The cardiorenal protection attributed to SGLT2 inhibitors is primarily thought to arise from hemodynamic actions, sustained by their natriuretic and osmotic effects. On the other hand, the protective effects of GLP-1 RA may be linked to anti-atherogenic and immune-modulating mechanisms.[39,40] Despite the prominence of SGLT2 inhibitors in the management of type 2 DM, their favorable impact on heart failure, major adverse cardiovascular events (MACE) and end-stage kidney disease appears to be largely independent of glycemic control.[41] Notably, evidence indicates that these drugs offer protection against heart failure hospitalization, reduce the incidence of MACE, and CKD progression even in individuals without diabetes. Furthermore, while the glucose-lowering efficacy of SGLT2 inhibitors diminishes with declining renal function, their safeguarding effects against end-stage kidney disease persist even into the later stages of CKD.[41] GLP-1 RA have been shown to reduce MACE, improve glycemic control, contribute to weight reduction, and lower CVD mortality. Also, the novel dual GIP/GLP-1 agonist Tirzepatide, by simultaneously activating two incretin-dependent pathways, exhibits a synergistic effect on glycemic and weight control. This dual activation proves to be significantly more effective in improving metabolic outcomes compared to selective GLP-1 RA.[42] Finerenone, a selective mineralocorticoid receptor (MR) antagonist, is recommended in CKD with diabetes, specifically in individuals with an estimated glomerular filtration rate (eGFR) greater than 25 ml/min.[43] This medication is known to reduce adverse kidney and cardiovascular events by exerting its cardiorenal protection at a distinct level. It targets MR overactivation, a significant pro-inflammatory and pro-fibrotic driver implicated in cardiorenal complications in type 2 DM.[43]

The recommended blood pressure target in CKM management is <130/80.[6] In CVD with CKD or diabetes with albuminuria, ACEIs or ARBs are advised. In African American patients, after optimizing guideline-directed medical therapy (GDMT) pillars, consider hydralazine/isosorbide, acknowledging potential variations in response to antihypertensive medications based on ethnicity.[6] Tailoring treatment to individual characteristics is crucial. For individuals with diabetes and ASCVD, initial lipid-lowering therapy typically involves high-intensity statins. Supported by clinical trial data, both American and European guidelines endorse the addition of ezetimibe, and if necessary, PCSK9 inhibitors.[32] In stage 4 CKM conditions, the reduction of ASCVD risk is recommended through the use of aspirin or P2Y12 inhibitors, in addition to high-intensity statins. In stage 2 CKM, where cardiovascular risk remains a concern, the introduction of ezetimibe is advised.[6] Ezetimibe is particularly beneficial as it contributes to a 50 % reduction in LDL cholesterol levels, thereby playing a crucial role in lowering the risk of ASCVD. Statin therapy is highlighted for its dual impact on lowering LDL cholesterol and reducing triglyceride levels by 10–30 %.[6] This multifaceted approach helps mitigate ASCVD risk, addressing both lipid components effectively. Furthermore, the inclusion of Icosapent ethyl is noted for its capacity to reduce cardiovascular events and mortality. This additional intervention adds to the comprehensive strategy aimed at managing the complex interplay of

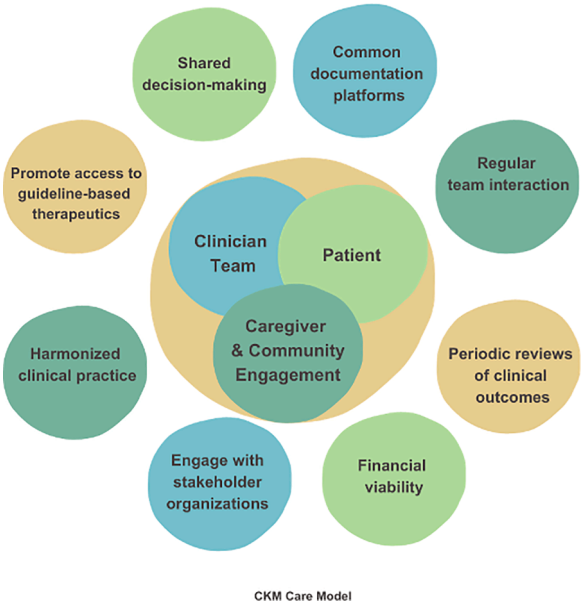

Fig. 3. Components of CKM multidisciplinary care model.[45]

cardiovascular, kidney, and metabolic aspects in CKM conditions. In the context of GDMT, trials focusing on GDMT for heart failure and CKD often lack sufficient representation, particularly for patients in advanced CKD stages (eGFR < 30 mL).[44] Additionally, there is limited guidance on interpreting fluctuating kidney function changes during decongestion and the initiation/titration of GDMT in HF. Consequently, more studies are imperative to effectively establish the role of GDMT in managing heart failure in patients with advanced CKD.

Integrated multidisciplinary approaches

A patient-centered integrated multidisciplinary approach can lead to improved outcomes, enhanced quality of life, and reduced healthcare costs. The development and implementation of these multidisciplinary care models are crucial steps in addressing the evolving landscape of healthcare for CKM syndrome. Successfully establishing these models necessitates collaborative initiatives spanning local, regional, and national organizations. Such collective efforts are imperative to instigate the required changes and ensure the long-term sustainability of these multidisciplinary care models.[45] A successful institutional cardio-renal-metabolic care model integrates a collaborative team, including physicians, dieticians, clinical pharmacists, care navigators, and administrative representatives from cardiology, nephrology, and endocrinology. It relies on shared decision-making, common documentation platforms, regular team interaction, and periodic reviews of clinical outcomes and financial viability (Fig. 3).[45] Patient and caregiver representation ensures alignment with patient-centered values and therapeutic goals. Ensuring harmonized clinical practices across specialties and promoting access to innovative therapies, such as SGLT2 inhibitors, GLP-1 RA, and other emerging treatments for cardio-renal-metabolic conditions, can be achieved by engaging payers, pharmacy benefit managers, and pharmaceutical companies. Involving these stakeholders in strategies for the efficient adoption of guideline-based treatments facilitates the successful delivery of integrated care for CKM, enhancing overall patient outcomes.[45]

Given the continuous and intricate cross-talk between the kidney and heart, compounded by the evolving clinical profiles of patients, there has been a pressing need for innovative approaches in addressing complex cardiorenal diseases.[46] Proposals have been abundant, suggesting the establishment of multidisciplinary frameworks to navigate this intricate interplay. A key recommendation involves the training of physicians in dedicated cardio nephrology tracks, aimed at refining the design of future studies in cardiorenal medicine and addressing a significant barrier in the field – patient recruitment.[46] To initiate this transformative process, the proposal includes the formation of an international multidisciplinary group tasked with crafting a comprehensive curriculum for such an educational program. This marks the foundational step towards advancing the understanding and management of the intricate dynamics between the heart and kidneys.[46] These efforts will expedite the translation of recent scientific discoveries, leading to improved health outcomes for patients with CKM syndrome.

Prevention and screening strategies

Early detection of health conditions with substantial negative clinical consequences represents a critical preventive public health opportunity, particularly in the presence of multiple effective therapeutics. A pivotal component of the CKM framework involves proactive screening in both the general population and clinical settings to identify individuals at various stages of the CKM syndrome.[6] Metabolic risk factor screening is grounded in the measurement of key parameters such as blood pressure, lipids, blood glucose, and anthropometric measures like BMI and waist circumference.[32] Evaluations of kidney function serve as complementary sources of prognostic information, guiding therapeutic approaches. However, there is limited evidence on the frequency, age of onset, and modalities for screening CKM risk factors. Screening for traditional risk factors is advised in healthy young adults every 4 to 6 years.[32] Given that obesity is central to CKM syndrome, annual BMI assessments are widely recommended. Evidence also supports glycemic assessments for the entire population, irrespective of BMI, to enhance equity in prediabetes and diabetes diagnosis.[47] Blood pressure screening is recommended every 3 to 5 years for individuals aged 18 to 39, and annually for those above 40.[48] The Endocrine Society suggests MetS assessments every 3 years for individuals with risk factors and yearly diabetes assessments for those with prediabetes.[49] The Kidney Disease Improving Global Outcomes recommends CKD assessments, including eGFR and albuminuria, providing crucial prognostic information for kidney and cardiovascular risk.[50] This is especially valuable in individuals with CKD and established metabolic risk factors such as diabetes and hypertension. However, additional studies are necessary to establish a definitive screening strategy for the prevention of CKM.

Early life prevention is another strategic approach discussed in the literature, with studies indicating that prenatal exposures can markedly influence the health of offspring in the context of CKM conditions. However, the impact of interventions aimed at improving maternal health on CKM profiles among children is not yet fully defined. Managing CKM risk factors during childhood and adolescence presents challenges as it necessitates considering the child, their community, and their environment for optimally effective therapeutic intervention. Given these complexities and the need for a more thorough understanding, future research becomes imperative.[51] Investigating the impact of maternal health interventions on CKM outcomes in children and refining strategies for managing CKM risk factors during early life stages will contribute significantly to preventive and therapeutic efforts in this field. Social Determinants of Health (SDOH) is another crucial aspect involved in the CKM syndrome. Interventions that include screening for social needs and connect patients to relevant services have shown reductions in the prevalence of social needs. Studies suggest that obtaining resources to address social needs related to aspects such as food, housing, medication, and transportation after screening has been associated with reductions in blood pressure, LDL cholesterol, and emergency room visits.[52] However, additional data is needed to establish and further understand these associations.

Conclusions

Cardiovascular, kidney, and metabolic diseases, such as type 2 DM, interact at the pathophysiological level, leading to a clinical overlap manifested in the broader Cardio-Renal-Metabolic (CKM) syndrome. These three health domains exhibit shared underlying mechanisms, the activation of which initiates a detrimental cycle, perpetuating disease processes and escalating morbidity and mortality. The intricate interplay of cardiovascular, kidney, and metabolic diseases highlights the necessity for targeted interventions that address their interconnected nature. Transitioning to a holistic approach with integrated multidisciplinary collaboration in CKM care, rather than isolated treatment of individual diseases, has the potential to break the vicious cycle and significantly improve overall health outcomes for patients. Further research is crucial to deepen our understanding of CKM pathophysiology. This involves clarifying bidirectional cardiovascular-kidney relationships, identifying biological factors influencing CKM risk, exploring social determinants and their interconnections, investigating genetic aspects of interethnic variations in CKM development, understanding drug mechanisms of action, validating risk scores for risk-stratified personalized care, addressing gaps in systematic CKM syndrome screening, and conducting outcomes trials to elucidate the benefits of integrated management for comorbid type 2 DM, CVD, and CKD. In addition, there is a critical need for clinical trials focused on specific populations within the CKM syndrome. These trials should encompass women, younger individuals, individuals from high-risk demographics such as Asian ethnic groups, and those in the realm of primary prevention. By addressing specific demographic groups, researchers can tailor interventions, shaping individualized treatment choices, and closing current gaps in CKM syndrome research.

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Sneha Annie Sebastian: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Inderbir Padda:** Writing – original draft. **Gurpreet Johal:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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